HETEROCYCLIC AMINE DNA BINDING AT LOW DOSES IN ANIMALS AND HUMANS.

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SUMMARY

Diet constitutes an important route of exposure to mutagenic compounds. Heterocyclic amines (HCAs), such as 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), are mutagenic and carcinogenic compounds formed during the cooking of protein rich foods. Human exposure to MeIQx via dietary sources has been estimated to range from a few ng/Kg/day to as high as ≈4 μg/Kg/day. In contrast, most rodent studies have been conducted at high doses, in excess of 10 mg/Kg/day. To bridge the gap between human exposure to MeIQx and the animal studies, we have investigated the dose-response of MeIQx in animals at low doses using the technique of accelerator mass spectrometry (AMS). In addition, we have begun to compare the adducts found in animals at low dose to adducts in humans given similar well-defined MeIQx doses. AMS is a nuclear physics technique for measuring isotope ratios with sensitivity in the attomole (10^{-18} moles) range for radiocarbon. It is ideal for such studies because it allows the use of very low isotope and chemical doses. MeIQx levels in various tissues and hepatic MeIQx-DNA adduct formation have been studied under both acute and chronic exposures in rodents. In order to make a direct species comparison, rodent colonic MeIQx-DNA adduct levels generated from an acute exposure have been compared to human colonic DNA adduct levels following oral administration of [^{14}C]-MeIQx. DNA digests from the human colon samples have been analyzed by high performance liquid chromatography/AMS for the spectrum of MeIQx-DNA adducts generated in rodent and human tissues. The results of these studies show: 1) In acute rat

dosing studies, the levels of orally administered MeIQx are highest in the liver, followed by the kidney, pancreas and intestine. Furthermore, MeIQx-DNA adducts formed in the liver increase in a linear fashion with administered dose of MeIQx. 2) Under chronic exposure conditions, MeIQx levels in the liver plateau after 7 days, however, MeIQx-DNA adducts accumulate for 30 days before steady-state levels are reached. (3) Steady-state DNA adduct levels displayed a linear dose response relationship. (4) Administration of a single oral dose of MeIQx to human volunteers resulted in 7-13 times higher colon DNA adduct levels than rodents at the equivalent dose 5) ≥90% of the MeIQx-DNA adducts found 6 hr after a single dose in both rodent and human colon appears to be the dG-C8 adduct. These results suggest that in rodent models the bioactive dose to target tissues is a linear function of administered dose down to anticipated human exposure levels. Furthermore, at an equivalent dose the human colon receives a higher biologically effective dose of MeIQx than does rodent colon. This data suggests that the use of rodent data may underestimate human risk by a factor of 10 if the bioactive dose to the colon represents a valid marker of tumorigenicity in both species.

This work performed under the auspices of the US DOE under contract W-7405-ENG-48 at LLNL and partially supported by NIH CA55861, USAMRDC #4559FLB and the United Kingdom Ministry of Agriculture Fisheries and Food. The authors thank Dr. R. Turesky (Nestec, Inc.) for providing the MeIQx-DNA adduct standards used in this work.